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=> d his nofil

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               SEL RN L1

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                  OR 1161-13-3/BI OR 1164-16-5/BI OR 1195-45-5/BI OR 129833-54-1
                 /BI OR 16588-69-5/BI OR 2018-61-3/BI OR 20780-76-1/BI OR
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                  OR 40397-98-6/BI OR 438576-16-0/BI OR 443-69-6/BI OR 4668-42-2
                 /BI OR 50528-86-4/BI OR 5241-58-7/BI OR 55289-36-6/BI OR
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                 744198-15-0/BI OR 744198-16-1/BI OR 744198-17-2/BI OR 744198-18
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L7            30 SEA ABB=ON  PLU=ON  L6 AND BR/ELS
L8             0 SEA ABB=ON  PLU=ON  L7 AND "BENZYL"
L9             0 SEA ABB=ON  PLU=ON  L7 AND "PHENYLETHYL"
L10            6 SEA ABB=ON  PLU=ON  L7 AND 2-10 C6/ES
               D SCA
L11            0 SEA ABB=ON  PLU=ON  L6 AND "CARBAMOYL"
L12        46521 SEA ABB=ON  PLU=ON  "CARBAMOYL"
               D 1-3
               D 3-6
L13        19617 SEA ABB=ON  PLU=ON  L12 AND NR<3
L14         2753 SEA ABB=ON  PLU=ON  L13 AND C<10
L15          114 SEA ABB=ON  PLU=ON  L14 AND O=1 AND N=1
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L18           14 SEA ABB=ON  PLU=ON  L17 NOT AL/ELS
L19         7135 SEA ABB=ON  PLU=ON  L12 NOT RSD/FA
L20          716 SEA ABB=ON  PLU=ON  L19 AND C<5
L21          141 SEA ABB=ON  PLU=ON  L20 AND C=3 AND NC=1
L22           42 SEA ABB=ON  PLU=ON  L21 NOT (S OR SE OR CL OR BR OR F OR GE OR
                 AL OR P)/ELS
L23            7 SEA ABB=ON  PLU=ON  L22 AND O=1 AND N=1
L24            5 SEA ABB=ON  PLU=ON  L23 AND C3H6NO/MF
                 D 1
                 D 2
                 D 3
L25       322861 SEA ABB=ON  PLU=ON  "CARBAMIC ACID"
L26            6 SEA ABB=ON  PLU=ON  L7 AND 2 C6/ES
L27          105 SEA ABB=ON  PLU=ON  C21H22BRN3O4/MF
L28            2 SEA ABB=ON  PLU=ON  L27 AND L2
                 D SCA
                 D 1-2

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L29              STR 744198-09-2
L30            6 SEA FAM FUL L29

     FILE 'HCAPLUS' ENTERED AT 17:41:36 ON 12 SEP 2006
L31            7 SEA ABB=ON  PLU=ON  L30

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FILE COVERS 1907 - 12 Sep 2006  VOL 145 ISS 12
FILE LAST UPDATED: 11 Sep 2006  (20060911/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L29              STR
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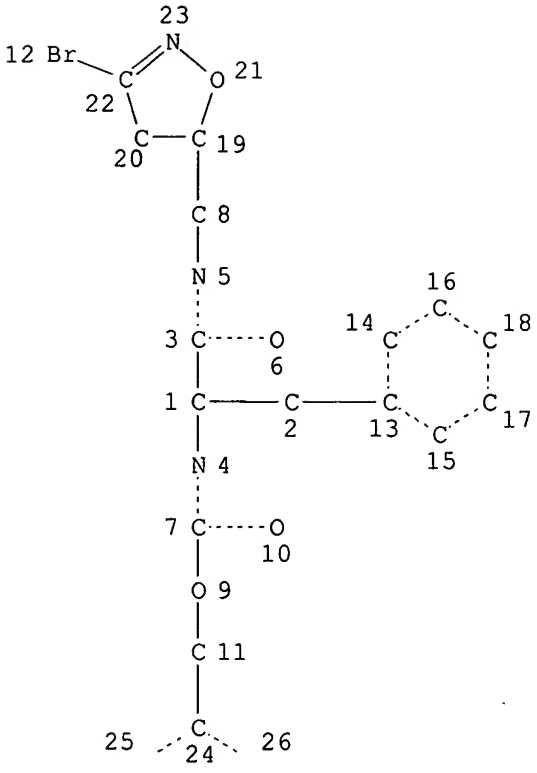

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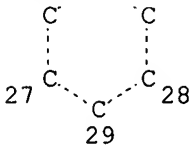

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE
L30 6 SEA FILE=REGISTRY FAM FUL L29
L31 7 SEA FILE=HCAPLUS ABB=ON PLU=ON L30

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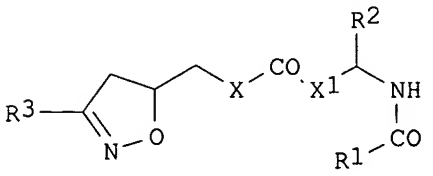
L31 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:217140 HCAPLUS
DOCUMENT NUMBER: 144:293068
TITLE: Preparation of dihydroisoxazole and isatin derivatives for use in pharmaceutical compositions as transglutaminase inhibitors

INVENTOR(S): Khosla, Chaitan; Watts, Richard Edward; Siegel, Matthew John; Pinkas, Daniel M.; Choi, Kihang; Rich, Keith M.
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior University, USA
SOURCE: U.S. Pat. Appl. Publ., 31 pp., Cont.-in-part of U.S. Ser. No. 716,846.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2006052308	A1	20060309	US 2005-213173		20050826
US 2004167069	A1	20040826	US 2003-716846		20031118
PRIORITY APPLN. INFO.:			US 2003-716846	A2	20031118
			US 2002-380761P	P	20020514
			US 2002-392782P	P	20020628
			US 2002-422933P	P	20021031
			US 2002-428033P	P	20021120
			WO 2003-US15343	A2	20030514

OTHER SOURCE(S): MARPAT 144:293068
GI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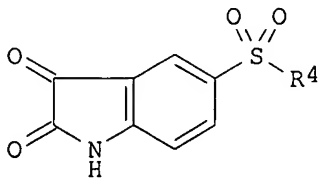
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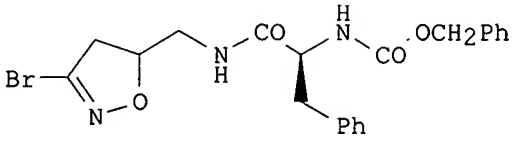
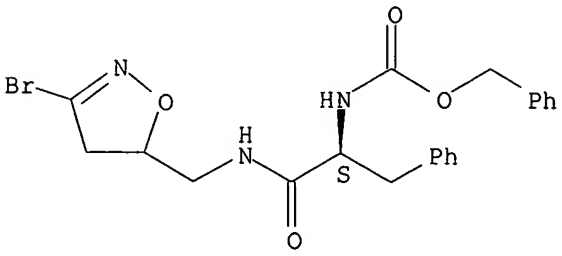

III

AB Transglutaminase (tTGase) inhibitors, such as I [R1, R2 = H, alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkoxy, alkylthio, halogen, etc.; R3 = Cl, Br; X = NH, O; X1 = (CH2)n, n = 0-10] and II [R4 = alkylamino, benzylamino, amino acid residue, etc.], were prepared for therapeutic use in the treatment of neurol. cancers. Thus, dihydroisoxazole phenylalanine derivative III was prepared with 52% yield by an amidation reaction of 3-bromo-5-aminomethyl-4,5-dihydroisoxazole with N-(benzyloxycarbonyl)-L-phenylalanine using HOBt in DMF. The prepared dihydroisoxazoles, isatins and peptides were tested for tTGase-2 inhibitory activity and for inhibition of astrocytoma, glioblastoma, and meningioma tumors.
IT **744198-09-2P 744198-15-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)
(preparation of dihydroisoxazole and isatin derivs. for use in pharmaceutical compns. as transglutaminase-2 inhibitors)

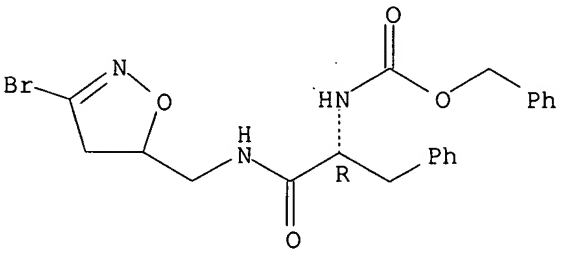
RN 744198-09-2 HCAPLUS
CN Carbamic acid, [(1S)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 744198-15-0 HCAPLUS
CN Carbamic acid, [(1R)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L31 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:356173 HCAPLUS
DOCUMENT NUMBER: 143:125809
TITLE: Chemistry and Biology of Dihydroisoxazole Derivatives: Selective Inhibitors of Human Transglutaminase 2
AUTHOR(S): Choi, Kihang; Siegel, Matthew; Piper, Justin L.; Yuan, Liya; Cho, Eun; Strnad, Pavel; Omary, Bishr; Rich, Keith M.; Khosla, Chaitan
CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, CA, 94305, USA
SOURCE: Chemistry & Biology (2005), 12(4), 469-475
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

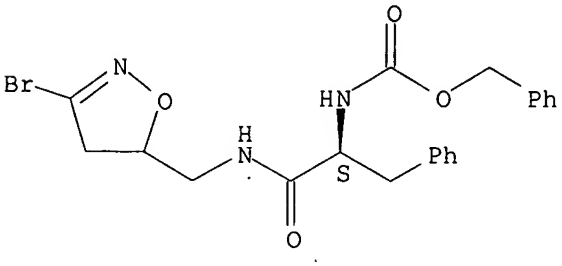
AB Summary: 3-Halo-4,5-dihydroisoxazoles are attractive warheads for the selective inhibition of nucleophilic active sites in biol. systems. A series of 3-bromo-4,5-dihydroisoxazole compds. were prepared and tested for their ability to irreversibly inhibit human transglutaminase 2 (TG2), an enzyme that plays an important role in the pathogenesis of diverse disorders including Celiac Sprue and certain types of cancers. Several

compds. showed high specificity for human TG2 (kinh/KI > 2000 min-1M-1) but essentially no reactivity (k < 1 min-1M-1) toward physiol. thiols such as glutathione. The pharmacokinetic and pharmacodynamic properties of a prototype dihydroisoxazole inhibitor, 1b, were evaluated; in mice the compound showed good oral bioavailability, short serum half-life and efficient TG2 inhibition in small intestinal tissue, and low toxicity. It also showed excellent synergism with N,N'-bis(2-chloroethyl)-N-nitrosourea (BCNU, carmustine) against refractory glioblastoma tumors in mice. A fluorescent dihydroisoxazole inhibitor 5 facilitated microscopic visualization of TG2 endocytosis from the extracellular surface of HCT-116 cells. Together, these findings demonstrate the promise of dihydroisoxazole compds. as probes for the biol. of TG2 and its role in human disease.

IT **744198-09-2 744198-15-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydroisoxazole derivs. as inhibitors of human transglutaminase)

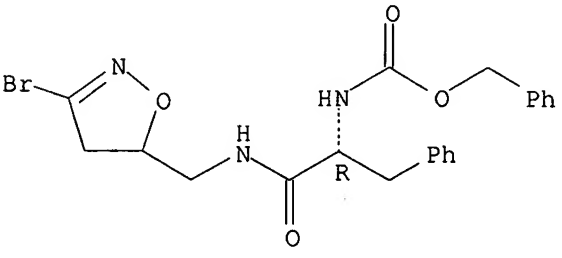
RN 744198-09-2 HCAPLUS
CN Carbamic acid, [(1S)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 744198-15-0 HCAPLUS
CN Carbamic acid, [(1R)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:703116 HCAPLUS
DOCUMENT NUMBER: 141:218994
TITLE: Tissue transglutaminase (tTGase) inhibitor therapy for celiac sprue and dermatitis herpetiformis

INVENTOR(S): Khosla, Chaitan; Choi, Kihang
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of Appl. No. PCT/US03/15343.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004167069	A1	20040826	US 2003-716846	20031118
CA 2487247	AA	20031127	CA 2003-2487247	20030514
WO 2003096979	A2	20031127	WO 2003-US15343	20030514
WO 2003096979	A3	20040212		
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EP 1507549	A2	20050223	EP 2003-728939	20030514
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WO 2005049064	A1	20050602	WO 2004-US37873	20041112
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2006035838	A1	20060216	US 2005-514177	20050628
US 2006052308	A1	20060309	US 2005-213173	20050826

PRIORITY APPLN. INFO.:

US 2002-380761P	P	20020514
US 2002-392782P	P	20020628
US 2002-422933P	P	20021031
US 2002-428033P	P	20021120
WO 2003-US15343	A2	20030514
US 2003-716846	A	20031118

APP. 6

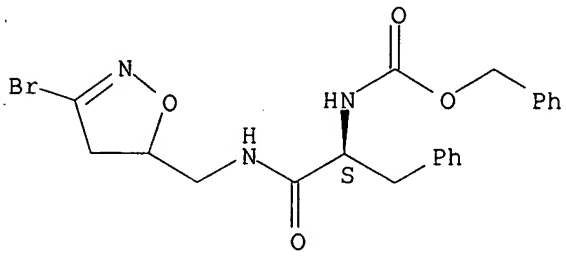
OTHER SOURCE(S): MARPAT 141:218994

AB Administering an ED of a tTGase inhibitor to a celiac sprue or dermatitis herpetiformis patient reduces the toxic effects of toxic gluten oligopeptides, thereby attenuating or eliminating the damaging effects of gluten. Preparation and tissue transglutaminase-inhibiting activity of dihydroisoxazole moiety-containing compds. is included.

IT **744198-09-2P 744198-15-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

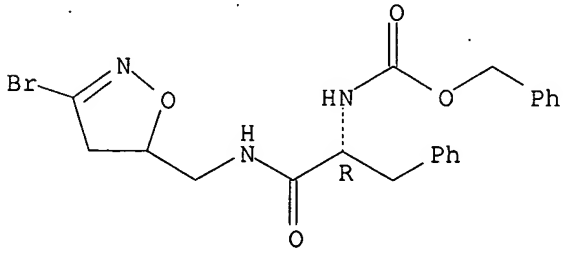
(Uses)
(tissue transglutaminase inhibitor therapy for celiac sprue and dermatitis herpetiformis)
RN 744198-09-2 HCAPLUS
CN Carbamic acid, [(1S)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 744198-15-0 HCAPLUS
CN Carbamic acid, [(1R)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



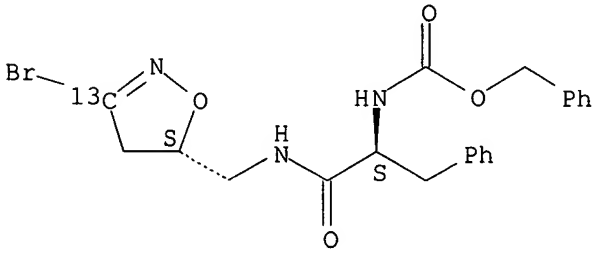
L31 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:444144 HCAPLUS
DOCUMENT NUMBER: 119:44144
TITLE: Solid-state carbon-13 NMR study of a transglutaminase-inhibitor adduct
AUTHOR(S): Auger, Michele; McDermott, Ann E.; Robinson, Valerie; Castelhano, Arlindo L.; Billedeau, Roland J.; Pliura, Diana H.; Krantz, Allen; Griffin, Robert G.
CORPORATE SOURCE: Francis Bitter Natl. Magnet Lab., Massachusetts Inst. Technol., Cambridge, MA, 02139, USA
SOURCE: Biochemistry (1993), 32(15), 3930-4
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Solid-state 13C NMR was used to study the structure of the adduct resulting from the inactivation of transglutaminase by 3-halo-4,5-dihydroisoxazoles. These inhibitors were conceived on the assumption that they would inhibit transglutaminase by attack of an enzyme active site cysteine SH group on the imine C atom of the dihydroisoxazole ring. The tetrahedral intermediate formed could then break down with the loss of the halide group and the subsequent formation of a stable imino

→ See later patent

thioether adduct. The 13C CPMAS NMR spectra of the chloro-, bromo-, and (ethylthio)dihydroisoxazole inhibitors were compared, and the results indicated that the chemical shift of the C-3 atom is sensitive to the nature of the heteroatom. Subtraction of the natural-abundance 13C solid-state NMR spectrum of the enzyme from that of the enzyme inactivated by C-3-labeled chlorodihydroisoxazole revealed a broad peak at 156 ppm. The chemical shift of this peak was very close to that observed for a model 3-ethylthio compound and suggested the formation of a stable imino thioether enzyme adduct. Similar results were obtained for lyophilized enzyme adducts and for frozen solns. of the enzyme adduct in the absence and presence of Ca2+. These results were compared with those obtained by solution NMR on an aqueous solution of the enzyme-inhibitor complex. The 13C-labeled C-3 resonance was not observed in this case.

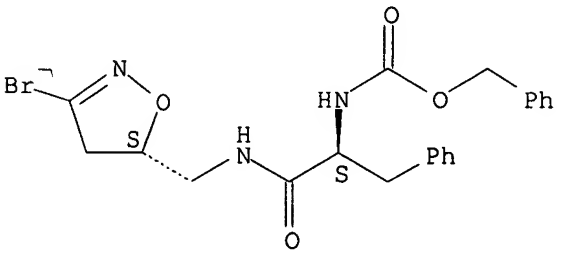
IT **148416-83-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 148416-83-5 HCAPLUS
CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl-3-13C)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



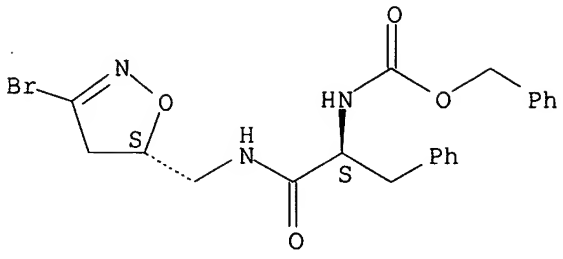
IT **120244-83-9 120244-83-9D**, transglutaminase adducts
RL: PRP (Properties)
(structure of, solid-state carbon-13 NMR study of)
RN 120244-83-9 HCAPLUS
CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 120244-83-9 HCAPLUS
CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L31 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:557401 HCAPLUS
DOCUMENT NUMBER: 117:157401
TITLE: Transglutaminase inhibitors as hair growth inhibitors
INVENTOR(S): Handelman, Joseph H.; Shander, Douglas; Funkhouser, Margaret G.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 9211007	A1	19920709	WO 1991-US9645	19911219
	W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, SD, SE, SU, US				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG				
→	US 5143925	A	19920901	US 1991-794321	19911112
	CA 2098102	AA	19920620	CA 1991-2098102	19911219
	CA 2098102	C	19961105		
	AU 9191653	A1	19920722	AU 1991-91653	19911219
	AU 656550	B2	19950209		
	EP 563301	A1	19931006	EP 1992-903695	19911219
	EP 563301	B1	20000510		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
	JP 06504057	T2	19940512	JP 1991-503400	19911219
	AT 192644	E	20000515	AT 1992-903695	19911219
	ES 2145005	T3	20000701	ES 1992-903695	19911219

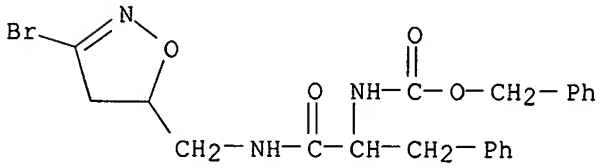
PRIORITY APPLN. INFO.: US 1990-632126 A1 19901220
WO 1991-US9645 A 19911219

AB The rate and character of mammalian hair growth is altered by topical application to the skin of a composition containing an inhibitor of the transglutaminase. A topical composition contained 5-(N-benzyloxycarbonyl-L-phenylalaninamido-methyl)-3-bromo-4,5-dihydroisoxazole 20, acetone 75, propylene carbonate 20, benzyl alc. 5%. The application of above composition on hamster skin for 18 days inhibited the hair mass by 87.87%.

IT **115329-49-2**
RL: BIOL (Biological study)
(as hair growth inhibitor, topical composition containing)

RN 115329-49-2 HCAPLUS

CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



L31 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:193339 HCAPLUS
DOCUMENT NUMBER: 110:193339
TITLE: Synthesis, chemistry, and absolute configuration of novel transglutaminase inhibitors containing a 3-halo-4,5-dihydroisoxazole
AUTHOR(S): Castelhano, Arlindo L.; Billedeau, Roland; Pliura, Diana H.; Bonaventura, Bonnie J.; Krantz, Allen
CORPORATE SOURCE: Syntex Inc., Mississauga, ON, L5N 3X4, Can.
SOURCE: Bioorganic Chemistry (1988), 16(3), 335-40
CODEN: BOCMBM; ISSN: 0045-2068
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 110:193339

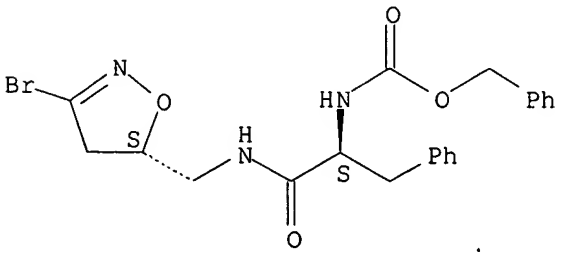
See patent

AB The preparation of potent transglutaminase inhibitors containing a 3-halo-4,5-dihydroisoxazole and the determination of their absolute configuration are described. Interestingly, reaction of halodihydroisoxazoles with thiolate is dependent on the nature of the halogen atom, with the bromide primarily undergoing ring cleavage and the chloride undergoing displacement with the ring intact. This result may have implications as regards mechanisms of transglutaminase inhibition by 3-halo-4,5-dihydroisoxazoles.

IT **120244-83-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(inactivation by, of transglutaminase)

RN 120244-83-9 HCAPLUS
CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

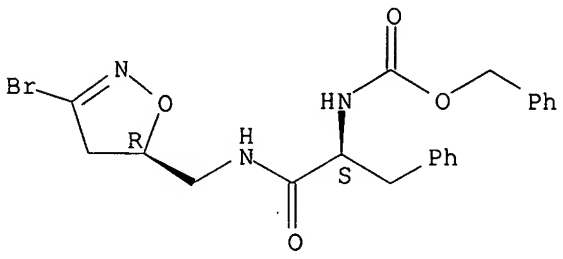
Absolute stereochemistry.



IT **120245-03-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 120245-03-6 HCAPLUS
CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L31 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:76070 HCAPLUS
DOCUMENT NUMBER: 110:76070
TITLE: Preparation and testing of amino acid amides of 5-(aminomethyl)-4,5-dihydroisoxazoles as transglutaminase inhibitors
INVENTOR(S): Castelhano, Arlindo L.; Krantz, Alexander; Pliura, Diana H.; Venuti, Michael C.; De Young, Lawrence M.
PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA
SOURCE: Eur. Pat. Appl., 95 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

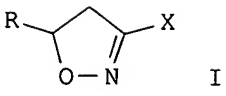
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
EP 237082	A2	19870916	EP 1987-103700		19870313
EP 237082	A3	19880914			
EP 237082	B1	19910529			
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE					
DK 8701303	A	19870915	DK 1987-1303		19870313
AU 8769987	A1	19870917	AU 1987-69987		19870313
AU 599636	B2	19900726			
JP 62252779	A2	19871104	JP 1987-59922		19870313
HU 44244	A2	19880229	HU 1987-1105		19870313
HU 201032	B	19900928			
ZA 8701860	A	19881026	ZA 1987-1860		19870313
US 4912120	A	19900327	US 1987-25451		19870313
IL 81887	A1	19910512	IL 1987-81887		19870313
IL 95264	A1	19910512	IL 1987-95264		19870313
AT 63906	E	19910615	AT 1987-103700		19870313
ES 2038609	T3	19930801	ES 1987-103700		19870313
US 4929630	A	19900529	US 1989-404791		19890908

PRIORITY APPLN. INFO.:

US 1986-839743	A	19860314
EP 1987-103700	A	19870313
IL 1987-81887	A	19870313
US 1987-25451	A3	19870313

OTHER SOURCE(S): CASREACT 110:76070; MARPAT 110:76070

GI



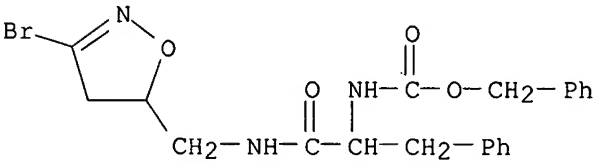
I

AB The title compds. [I; R = R1R2NCHR3CONHCH2, R2 = NHCH2; NR1R2 = phthalimido; R1R3 = (CH2)3, CH2CH(OH)CH2; R1 = H, Me; R2 = H, alkyl, lower alkylsulfonyl, (lower alkyl)arylsulfonyl, 9-fluorenylmethyloxycarbonyl, succinyl, cinnamoyl, CHO, alkanoyl, amino acid residue, etc.; R3 = H, lower alkyl, CHMeOCH2Ph, CH2CONH2, (CH2)2NH2, (CH2)4NHCO2CMe3, (CH2)2CH(OH)CH2NH2, (un)substituted phenylalkyl, etc.; X = halo, OR4, SR4, S(O)R4, SO2R4, SO2NH2, SO2NHR4; R4 = lower alkyl, fluorinated C2-3 alkyl, (un)substituted aryl, (un)substituted NH2, 1H-imidazol-1-yl] (II), useful as transglutaminase inhibitors, were prepared To a solution of 700 mg N-benzyloxycarbonyl-L-phenylalanine allyl amide in EtOAc/H2O was added NaHCO3 and in small portions 631 mg dibromoformaldoxime. The progress of the reaction was monitored by thin layer chromatog. and after completion of the reaction (2-4 h) the mixture was worked up to give I (R = CBZ-Phe, X = Br) (IV). A gel consisting of IV, 2.5% Klurel, 10% diisopropyl adipate, 80% EtOH and 5% polyethylene glycol was applied once daily to two dogs for 14 days, resulting in clearing of majority of blackhead-like lesions as well as many whitehead-like lesions. A gel formulation containing 1 IV, 3 H2O, 2 Carbopol, 0.01 Pr gallate, and 0.01% edetate disodium in 100 mL propylene glycol was given.

IT **115329-49-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as transglutaminase inhibitor)

RN 115329-49-2 HCAPLUS

CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



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PROCESSING COMPLETED FOR L34
PROCESSING COMPLETED FOR L40
PROCESSING COMPLETED FOR L41
L42          38 DUP REM L34 L40 L41 (66 DUPLICATES REMOVED)
                ANSWERS '1-31' FROM FILE HCAPLUS
                ANSWERS '32-33' FROM FILE MEDLINE
                ANSWER '34' FROM FILE EMBASE
                ANSWERS '35-38' FROM FILE BIOSIS

=> d l42 ibib abs 1-38

L42  ANSWER 1 OF 38  HCAPLUS  COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2006:217140  HCAPLUS
DOCUMENT NUMBER:          144:293068
TITLE:                    Preparation of dihydroisoxazole and isatin derivatives
                          for use in pharmaceutical compositions as
                          transglutaminase inhibitors
INVENTOR(S):              Khosla, Chaitan; Watts, Richard Edward;
                          Siegel, Matthew John; Pinkas, Daniel M.; Choi,
                          Kihang; Rich, Keith M.
PATENT ASSIGNEE(S):       The Board of Trustees of the Leland Stanford Junior
                          University, USA
SOURCE:                   U.S. Pat. Appl. Publ., 31 pp., Cont.-in-part of U.S.
                          Ser. No. 716,846.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   5
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     US 2006052308         A1    20060309    US 2005-213173           20050826
     US 2004167069         A1    20040826    US 2003-716846           20031118
PRIORITY APPLN. INFO.:                       US 2003-716846      A2   20031118
                                             US 2002-380761P     P    20020514
                                             US 2002-392782P     P    20020628
                                             US 2002-422933P     P    20021031
                                             US 2002-428033P     P    20021120
                                             WO 2003-US15343     A2   20030514
OTHER SOURCE(S):          MARPAT 144:293068
GI
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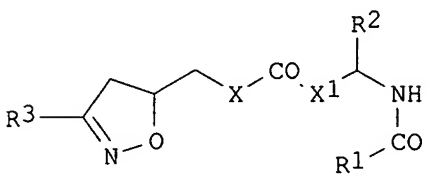

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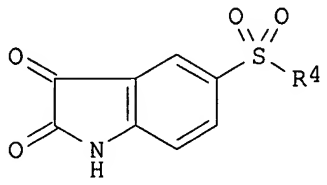
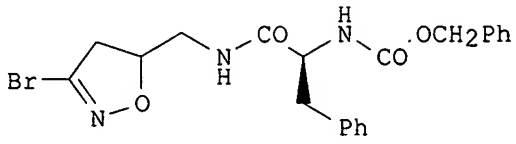


II



III

AB Transglutaminase (tTGase) inhibitors, such as I [R1, R2 = H, alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkoxy, alkylthio, halogen, etc.; R3 = Cl, Br; X = NH, O; X1 = (CH2)n, n = 0-10] and II [R4 = alkylamino, benzylamino, amino acid residue, etc.], were prepared for therapeutic use in the treatment of neurol. cancers. Thus, dihydroisoxazole phenylalanine derivative III was prepared with 52% yield by an amidation reaction of 3-bromo-5-aminomethyl-4,5-dihydroisoxazole with N-(benzyloxycarbonyl)-L-phenylalanine using HOBt in DMF. The prepared dihydroisoxazoles, isatins and peptides were tested for tTGase-2 inhibitory activity and for inhibition of astrocytoma, glioblastoma, and meningioma tumors.

L42 ANSWER 2 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2006:362104 HCAPLUS
DOCUMENT NUMBER: 144:404112
TITLE: Pharmacologic transglutaminase inhibition attenuates drug-primed liver hypertrophy but not Mallory body formation
AUTHOR(S): Strnad, Pavel; Siegel, Matthew; Toivola, Diana M.; **Choi, Kihang**; Kosek, Jon C.; **Khosla, Chaitan**; Omary, M. Bishr
CORPORATE SOURCE: Department of Medicine, Palo Alto VA Medical Center, Palo Alto, CA, 94304, USA
SOURCE: FEBS Letters (2006), 580(9), 2351-2357
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mallory bodies (MBs) are characteristic of several liver disorders, and consist primarily of keratins with transglutaminase-generated keratin crosslinks. We tested the effect of the transglutaminase-2 (TG2) inhibitor KCC009 on MB formation in a mouse model fed 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC). KCC009 decreased DDC-induced liver enlargement without affecting MB formation or extent of liver injury. TG2 protein and activity increased after DDC feeding and localized within and outside hepatocytes. KCC009 inhibited DDC-induced hepatomegaly by affecting hepatocyte cell size rather than proliferation. Hence, TG2 is a potential mediator of injury-induced hepatomegaly via modulation of hepatocyte hypertrophy, and KCC009-mediated TG2 inhibition does not affect mouse MB formation.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 3 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2006:87581 HCAPLUS
DOCUMENT NUMBER: 144:310329
TITLE: Inhibition of HLA-DQ2-Mediated Antigen Presentation by Analogues of a High Affinity 33-Residue Peptide from α2-Gliadin
AUTHOR(S): Xia, Jiang; Siegel, Matthew; Bergseng, Elin; Sollid, Ludvig M.; **Khosla, Chaitan**
CORPORATE SOURCE: Departments of Chemistry Chemical Engineering and Biochemistry, Stanford University, Stanford, CA, 94305-5025, USA
SOURCE: Journal of the American Chemical Society (2006), 128(6), 1859-1867
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human leukocyte antigen DQ2 is a class II major histocompatibility complex protein that plays a critical role in the pathogenesis of **Celiac Sprue** by binding to epitopes derived from dietary gluten and triggering the inflammatory response of disease-specific T cells. Inhibition of DQ2-mediated antigen presentation in the small intestinal mucosa of **Celiac Sprue** patients therefore represents a potentially attractive mode of therapy for this widespread but unmet medical need. Starting from a pro-inflammatory, proteolytically resistant, 33-residue peptide, LQLQPFPQPELPYPQPELPYPQPELPYPQPQPF, the authors embarked upon a systematic effort to dissect the relationships between peptide structure and DQ2 affinity and to translate these insights into prototypical DQ2 blocking agents. Three structural determinants within the first 20 residues of this 33-mer peptide, including a PQPELPYPQ epitope, its N-terminal flanking sequence, and a downstream Glu residue, were important for DQ2 binding. Guided by the x-ray crystal structure of DQ2, the L11 and L18 residues in the truncated 20-mer analog were replaced with sterically bulky groups to retain high DQ2 affinity but abrogate T cell recognition. A dimeric ligand, synthesized by regiospecific coupling of the 20-mer peptide with a bifunctional linker, was identified as an especially potent DQ2 binding agent. Two such ligands were able to attenuate the proliferation of disease-specific T cell lines in response to gluten antigens and, therefore, represent prototypical examples of pharmacol. suitable DQ2 blocking agents for the potential treatment of **Celiac Sprue.**
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 4 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2006:898345 HCAPLUS
TITLE: Effect of barley endoprotease EP-B2 on gluten digestion in the intact rat
AUTHOR(S): Gass, Jonathan; Vora, Harmit; Bethune, Michael T.; Gray, Gary M.; **Khosla, Chaitan**
CORPORATE SOURCE: Celiac Sprue Research Foundation, Palo Alto, CA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2006), 318(3), 1178-1186
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Celiac Sprue** is a multifactorial disease characterized by an intestinal inflammatory response to ingested gluten. Proteolytically resistant gluten peptides from wheat, rye, and barley persist in the intestinal lumen and elicit an immune response in genetically susceptible individuals. Here, we demonstrate the in vivo ability of a gluten-digesting protease ("glutenase") to accelerate the breakdown of a gluten-rich solid meal. The proenzyme form of endoprotease B, isoform 2 from Hordeum vulgare (EP-B2), was orally administered to adult rats with a solid meal containing 1 g of gluten. Gluten digestion in the stomach and small intestine was monitored as a function of enzyme dose and time by high-performance liquid chromatog. and mass spectrometry. In the absence of supplementary EP-B2, gluten was solubilized and proteolyzed to a limited extent in the stomach and was hydrolyzed and assimilated mostly in the small intestine. In contrast, EP-B2 was remarkably effective at digesting gluten in the rat stomach in a dose- and time-dependent fashion. At a 1:25 EP-B2/gluten dose, the gastric concentration

of the highly immunogenic 33-mer gliadin peptide was reduced by more than 50-fold within 90 min with no overt signs of toxicity. Evaluation of EP-B2 as an adjunct to diet control is therefore warranted in celiac patients.

L42 ANSWER 5 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2006:595926 HCAPLUS
DOCUMENT NUMBER: 145:224646
TITLE: Rational Design of Combination Enzyme Therapy for **Celiac Sprue**
AUTHOR(S): Siegel, Matthew; Bethune, Michael T.; Gass, Jonathan; Ehren, Jennifer; Xia, Jiang; Johannsen, Alexandre; Stuge, Tor B.; Gray, Gary M.; Lee, Peter P.; **Khosla, Chaitan**
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, CA, 94305, USA
SOURCE: Chemistry & Biology (Cambridge, MA, United States) (2006), 13(6), 649-658
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Celiac sprue** (also known as celiac disease) is an inheritable, gluten-induced enteropathy of the upper small intestine with an estimated prevalence of 0.5%-1% in most parts of the world. The ubiquitous nature of food gluten, coupled with inadequate labeling regulations in most countries, constantly poses a threat of disease exacerbation and relapse for patients. Here, the authors demonstrate that a two-enzyme cocktail comprised of a glutamine-specific cysteine protease (EP-B2) that functions under gastric conditions and a PEP, which acts in concert with pancreatic proteases under duodenal conditions, is a particularly potent candidate for **celiac sprue** therapy. At a gluten:EP-B2:PEP weight ratio of 75:3:1, grocery store gluten is fully detoxified within 10 min of simulated duodenal conditions, as judged by chromatog. anal., biopsy-derived T cell proliferation assays, and a com. antigluten antibody test.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 6 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2006:595925 HCAPLUS
TITLE: Heterologous Expression, Purification, Refolding, and Structural-Functional Characterization of EP-B2, a Self-Activating Barley Cysteine Endoprotease
AUTHOR(S): Bethune, Michael T.; Strop, Pavel; Tang, Yinyan; Sollid, Ludvig M.; **Khosla, Chaitan**
CORPORATE SOURCE: Department of Biochemistry, Stanford University, Stanford, CA, 94305, USA
SOURCE: Chemistry & Biology (Cambridge, MA, United States) (2006), 13(6), 637-647
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We describe the heterologous expression in Escherichia coli of the proenzyme precursor to EP-B2, a cysteine endoproteases from germinating barley seeds. High yields (50 mg/l) of recombinant proEP-B2 were obtained from E. coli inclusion bodies in shake flask cultures following purification and refolding. The zymogen was rapidly auto-activated to its mature form

under acidic conditions at a rate independent of proEP-B2 concentration, suggesting a cis mechanism of auto-activation. Mature EP-B2 was stable and active over a wide pH range and efficiently hydrolyzed a recombinant wheat gluten protein, α2-gliadin, at sequences with known immunotoxicity in **celiac sprue** patients. The X-ray crystal structure of mature EP-B2 bound to leupeptin was solved to 2.2 Å resolution and provided atomic insights into the observed subsite specificity of the endoproteases. Our findings suggest that orally administered proEP-B2 may be especially well suited for treatment of **celiac sprue**.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 7 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 2005:131071 HCAPLUS
DOCUMENT NUMBER: 142:372105
TITLE: Equilibrium and Kinetic Analysis of the Unusual Binding Behavior of a Highly Immunogenic Gluten Peptide to HLA-DQ2
AUTHOR(S): Xia, Jiang; Sollid, Ludvig M.; **Khosla, Chaitan**
CORPORATE SOURCE: Departments of Chemistry, Chemical Engineering, and Biochemistry, Stanford University, Stanford, CA, 94305, USA
SOURCE: Biochemistry (2005), 44(11), 4442-4449
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB HLA-DQ2 predisposes an individual to **celiac sprue** by presenting peptides from dietary gluten to intestinal CD4+ T cells. A selectively deamidated multivalent peptide from gluten (LQLQPFPQPELPYPQPELPYPQPELPYPQPQPF; underlined residues correspond to posttranslational Q → E alterations) is a potent trigger of DQ2 restricted T cell proliferation. Here the authors report equilibrium and kinetic measurements of interactions between DQ2 and (i) this highly immunogenic multivalent peptide, (ii) its individual constituent epitopes, (iii) its nondeamidated precursor, and (iv) a reference high-affinity ligand of HLA-DQ2 that is not recognized by gluten-responsive T cells from **celiac sprue** patients. The deamidated 33-mer peptide efficiently exchanges with a preloaded peptide in the DQ2 ligand-binding groove at pH 5.5 as well as pH 7.3, suggesting that the peptide can be presented to T cells comparably well through the endocytic pathway or via direct loading onto extracellular HLA-DQ2. In contrast, the monovalent peptides, and the nondeamidated precursor, as well as the tight-binding reference peptide show a much poorer ability to exchange with a preloaded peptide in the DQ2 binding pocket, especially at pH 7.3, suggesting that endocytosis of these peptides is a prerequisite for T cell presentation. At pH 5.5 and 7.3, dissociation of the deamidated 33-mer peptide from DQ2 is much slower than dissociation of its constituent monovalent epitopes or the nondeamidated precursor but faster than dissociation of the reference high-affinity peptide. Oligomeric states involving multiple copies of the DQ2 heterodimer bound to a single copy of the multivalent 33-mer peptide are not observed Together, these results suggest that the remarkable antigenicity of the 33-mer gluten peptide is primarily due to its unusually efficient ability to displace existing ligands in the HLA-DQ2 binding pocket, rather than an extremely low rate of dissociation

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 8 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2005:247316 HCAPLUS
DOCUMENT NUMBER: 142:443700
TITLE: Structural and mechanistic analysis of two prolyl endopeptidases: role of interdomain dynamics in catalysis and specificity
AUTHOR(S): Shan, Lu; Mathews, Irimpan I.; **Khosla, Chaitan**
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, CA, 94305, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2005), 102(10), 3599-3604
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Prolyl endopeptidases (PEPs) are a unique class of serine proteases with considerable therapeutic potential for the treatment of **celiac sprue**. The crystal structures of two didomain PEPs have been solved in alternative configurations, thereby providing insights into the mode of action of these enzymes. The structure of the Sphingomonas capsulata PEP, solved and refined to 1.8-Å resolution, revealed an open configuration of the active site. In contrast, the inhibitor-bound PEP from Myxococcus xanthus was crystallized (1.5-Å resolution) in a closed form. Comparative anal. of the two structures highlights a critical role for the domain interface in regulating interdomain dynamics and substrate specificity. Structure-based mutagenesis of the M. xanthus PEP confirms an important role for several interfacial residues. A salt bridge between Arg-572 and Asp-196/Glu-197 appears to act as a latch for opening or closing the didomain enzyme, and Arg-572 and Ile-575 may also help secure the incoming peptide substrate to the open form of the enzyme. Arg-618 and Asp-145 are responsible for anchoring the invariant proline residue in the active site of this postproline-cleaving enzyme. A model is proposed for the docking of a representative substrate PQPQLPYPQPQLP in the active site, where the N-terminal substrate residues interact extensively with the catalytic domain, and the C-terminal residues stretch into the propeller domain. Given the promise of the M. xanthus PEP as an oral therapeutic enzyme for treating **celiac sprue**, our results provide a strong foundation for further optimization of the PEP's clin. useful features.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 9 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 2005:800702 HCAPLUS
DOCUMENT NUMBER: 143:324617
TITLE: Identification and Analysis of Multivalent Proteolytically Resistant Peptides from Gluten: Implications for **Celiac Sprue**
AUTHOR(S): Shan, Lu; Qiao, Shuo-Wang; Arentz-Hansen, Helene; Molberg, Oeyvind; Gray, Gary M.; Sollid, Ludvig M.; **Khosla, Chaitan**
CORPORATE SOURCE: Departments of Chemical Engineering, Medicine, Chemistry and Biochemistry, Stanford University, Stanford, CA, 94305-5025, USA
SOURCE: Journal of Proteome Research (2005), 4(5), 1732-1741
CODEN: JPROBS; ISSN: 1535-3893
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Dietary gluten proteins from wheat, rye, and barely are the primary triggers for the immuno-pathogenesis of **Celiac Sprue**, a widespread immune disease of the small intestine. Recent mol. and structural analyses of representative gluten proteins, most notably α- and γ-gliadin proteins from wheat, have improved the authors' understanding of these pathogenic mechanisms. In particular, based on the properties of a 33-mer peptide, generated from α-gliadin under physiol. conditions, a link between digestive resistance and inflammatory character of gluten has been proposed. Here, the authors report three lines of investigation in support of this hypothesis. First, biochem. and immunol. anal. of deletion mutants of α-2 gliadin confirmed that the DQ2 restricted T cell response to the α-2 gliadin are directed toward the epitopes clustered within the 33-mer. Second, proteolytic anal. of a representative γ-gliadin led to the identification of another multivalent 26-mer peptide that was also resistant to further gastric, pancreatic and intestinal brush border degradation, and was a good substrate of human transglutaminase 2 (TG2). Analogous to the 33-mer, the synthetic 26-mer peptide displayed markedly enhanced T cell antigenicity compared to monovalent control peptides. Finally, in silico anal. of the gluten proteome led to the identification of at least 60 putative peptides that share the common characteristics of the 33-mer and the 26-mer peptides. Together, these results highlight the pivotal role of physiol. generated, proteolytically stable, TG2-reactive, multivalent peptides in the immune response to dietary gluten in **Celiac Sprue** patients. Prolyl endopeptidase treatment was shown to abolish the antigenicity of both the 33-mer and the 26-mer peptides, and was also predicted to have comparable effects on other proline-rich putatively immunotoxic peptides identified from other polypeptides within the gluten proteome.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 10 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2005:1064565 HCAPLUS

DOCUMENT NUMBER: 144:246627

TITLE: Tissue transglutaminase 2 inhibition promotes cell death and chemosensitivity in glioblastomas

AUTHOR(S): Yuan, Liya; **Choi, Kihang**; **Khosla, Chaitan**; Zheng, Xiao; Higashikubo, Ryuji; Chicoine, Michael R.; Rich, Keith M.

CORPORATE SOURCE: Department of Neurological Surgery, Washington University School of Medicine, St. Louis, MO, USA

SOURCE: Molecular Cancer Therapeutics (2005), 4(9), 1293-1302 CODEN: MCTOCF; ISSN: 1535-7163

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Tissue transglutaminase 2 belongs to a family of transglutaminase proteins that confers mech. resistance from proteolysis and stabilizes proteins. Transglutaminase 2 promotes transamidation between glutamine and lysine residues with the formation of covalent linkages between proteins. Transglutaminase 2 also interacts and forms complexes with proteins important in extracellular matrix organization and cellular adhesion. We have identified the novel finding that treatment of glioblastoma cells with transglutaminase 2 inhibitors promotes cell death and enhances sensitivity to chemotherapy. Treatment with either the competitive transglutaminase 2 inhibitor, monodansylcadaverine, or with highly specific small-mol. transglutaminase 2 inhibitors, KCA075 or KCC009,

results in induction of apoptosis in glioblastoma cells. Treatment with these transglutaminase 2 inhibitors resulted in markedly decreased levels of the prosurvival protein, phosphorylated Akt, and its downstream targets. These changes promote a proapoptotic profile with altered levels of multiple intracellular proteins that determine cell survival. These changes include decreased levels of the antiapoptotic proteins, survivin, phosphorylated Bad, and phosphorylated glycogen synthetase kinase 3β (GSK-3β), and increased levels of the proapoptotic BH3-only protein, Bim. In vivo studies with s.c. murine DBT glioblastoma tumors treated with transglutaminase 2 inhibitors combined with the chemotherapeutic agent, N-N'-bis (2-chloroethyl)-N-nitrosourea (BCNU), decreased tumor size based on weight by 50% compared with those treated with BCNU alone. Groups treated with transglutaminase 2 inhibitors showed an increased incidence of apoptosis determined with deoxynucleotidyl transferase-mediated biotin nick-end labeling staining. These studies identify inhibition of transglutaminase 2 as a potential target to enhance cell death and chemosensitivity in glioblastomas.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 11 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 2005:798933 HCAPLUS
DOCUMENT NUMBER: 143:405170
TITLE: Effect of pretreatment of food gluten with prolyl endopeptidase on gluten-induced malabsorption in **celiac sprue**
AUTHOR(S): Pyle, Gail G.; Paaso, Brian; Anderson, Barbara E.; Allen, Diane D.; Marti, Thomas; Li, Qing; Siegel, Matthew; **Khosla, Chaitan**; Gray, Gary M.
CORPORATE SOURCE: Celiac Sprue Research Foundation, Palo Alto, USA
SOURCE: Clinical Gastroenterology and Hepatology (2005), 3(7), 687-694
CODEN: CGHLAW; ISSN: 1542-3565
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We sought to determine whether prolyl endopeptidase (PEP) treatment of food gluten would obviate the intestinal dysfunction produced by small amts. of dietary gluten supplement in patients with **celiac sprue**. Twenty asymptomatic patients with histol. proven **celiac sprue** completed a randomized, double-blind, cross-over study involving two 14-day stages. Each patient consumed a low dose of a gluten supplement daily (5 g; equivalent to 1 slice of bread) in 1 stage and gluten pretreated with PEP in the other stage. Patients completed a daily symptom questionnaire and a D-xylose urine excretion and a 72-h quant. fecal fat were monitored before and after each stage. Results: Despite clin. remission at baseline, 40% of patients had at least 1 abnormal celiac antibody, 20% had an abnormal urine xylose, and 63% had an abnormal fecal fat test result. There was no difference in symptoms as a function of the type of gluten consumed. In response to gluten not treated with PEP, an appreciable proportion of patients developed malabsorption of fat (7 of 17, 41%) or xylose (8 of 14, 57%). When the gluten was pretreated with PEP, fat malabsorption was avoided in 5 of 7 and xylose malabsorption in 4 of 8 of these same patients. Conclusions: A significant proportion of asymptomatic patients with **celiac sprue** have abnormal celiac antibodies and fat or carbohydrate malabsorption. Pretreatment of gluten with PEP avoided the development of fat or carbohydrate malabsorption in the majority of those patients who developed fat or carbohydrate malabsorption after a 2-wk gluten challenge.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 12 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 2005:798932 HCAPLUS
DOCUMENT NUMBER: 143:345070
TITLE: Low-dose gluten challenge in **celiac sprue**: malabsorptive and antibody responses
AUTHOR(S): Pyle, Gail G.; Paaso, Brian; Anderson, Barbara E.; Allen, Diane; Marti, Thomas; **Khosla, Chaitan**; Gray, Gary M.
CORPORATE SOURCE: Celiac Sprue Research Foundation, Palo Alto, USA
SOURCE: Clinical Gastroenterology and Hepatology (2005), 3(7), 679-686
CODEN: CGHLAW; ISSN: 1542-3565
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Undiagnosed patients with symptoms of **celiac sprue** often present to physicians after establishing dietary gluten exclusion. Although they must resume a gluten-containing diet for evaluation, there are no guidelines regarding duration of the gluten challenge, gluten dose, or monitoring parameters. We investigated the effects of a short-term gluten challenge in asymptomatic treated adult celiac patients on intestinal absorption and celiac antibody tests. Eight adult asymptomatic celiac patients consumed either 5 or 10 g of partially hydrolyzed gluten per day in an orange juice mixture for 21 days while maintaining their usual gluten-free diet. A symptom questionnaire, serum antibodies (antigliadin Ig [Ig]A and anti-transglutaminase IgA and IgG), D-xylose urine excretion test, and 72-h quant. fecal fat test were monitored. Two patients (25%) had at least 1 abnormal celiac antibody test at baseline. There was no increase in antibodies during gluten exposure compared with baseline for any of the patients ($P > .05$). At baseline, 1 patient had abnormal urine xylose excretion, and 3 patients had abnormal fecal fat values. At day 15 of gluten challenge, all patients had reduced xylose absorption compared with baseline ($P = .0019$), and 5 of 8 participants (63%) reduced their xylose excretion to the abnormal range. Seven of 8 patients (88%) had increased fecal fat excretion at day 15 ($P = .026$), and 6 of these (75%) had steatorrhea by day 15. Short-term gluten challenge in asymptomatic adult celiac patients produces carbohydrate and fat malabsorption but does not increase transglutaminase and antigliadin antibody titers.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 13 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 13
ACCESSION NUMBER: 2005:1309547 HCAPLUS
DOCUMENT NUMBER: 144:252666
TITLE: Fermentation, purification, formulation, and pharmacological evaluation of a prolyl endopeptidase from Myxococcus xanthus: Implications for **Celiac Sprue** therapy
AUTHOR(S): Gass, Jonathan; Ehren, Jennifer; Strohmeier, Gregg; Isaacs, Indu; **Khosla, Chaitan**
CORPORATE SOURCE: Celiac Sprue Research Foundation, Palo Alto, CA, 94306-1193, USA
SOURCE: Biotechnology and Bioengineering (2005), 92(6), 674-684
CODEN: BIBIAU; ISSN: 0006-3592
PUBLISHER: John Wiley & Sons, Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Celiac Sprue** is a multi-factorial disease characterized by an inflammatory response to ingested wheat gluten and similar proteins in rye and barley. Proline-rich gluten peptides from wheat, rye, and barley are relatively resistant to gastrointestinal digestion, and therefore persist in the intestinal lumen to elicit immunopathol. in genetically susceptible individuals. In this study, we characterize the in vitro gluten detoxifying properties of a therapeutically promising prolyl endopeptidase from Myxococcus xanthus (MX PEP), and describe the development of a prototypical enteric-coated capsule containing a pharmacol. useful dose of this enzyme. A high-cell d. fed-batch fermentation process was developed for overprodn. of recombinant MX PEP in E. coli, yielding 0.25-0.4 g/L purified protein. A simple, scalable purification and lyophilization procedure was established that yields >95% pure, highly active and stable enzyme as a dry powder. The dry powder was blended with excipients and encapsulated in a hard gelatin capsule. The resulting capsule was enteric coated using Eudragit L30-D55 polymer coat, which provided sufficient resistance to gastric conditions (> 1 h in 0.01 M HCl, pH 2 with pepsin) and rapid release under duodenal conditions (15-30 min release in pH 6.0 in the presence of trypsin and chymotrypsin). In conjunction with pancreatic enzymes, MX PEP breaks down whole gluten into a product mixture that is virtually indistinguishable from that generated by the Flavobacterium meningosepticum (FM) PEP as judged by chromatog. assays. Competitive studies involving selected immunogenic peptides mixed with whole gluten reveal that both PEPs have a wide range of substrate specificity. Our results support further in vitro and in vivo evaluation of the MX PEP capsule as an oral therapeutic agent for **Celiac Sprue** patients.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 14 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 14
ACCESSION NUMBER: 2005:356173 HCAPLUS
DOCUMENT NUMBER: 143:125809
TITLE: Chemistry and Biology of Dihydroisoxazole Derivatives: Selective Inhibitors of Human Transglutaminase 2
AUTHOR(S): **Choi, Kihang**; Siegel, Matthew; Piper, Justin L.; Yuan, Liya; Cho, Eun; Strnad, Pavel; Omary, Bishr; Rich, Keith M.; **Khosla, Chaitan**
CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, CA, 94305, USA
SOURCE: Chemistry & Biology (2005), 12(4), 469-475
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Summary: 3-Halo-4,5-dihydroisoxazoles are attractive warheads for the selective inhibition of nucleophilic active sites in biol. systems. A series of 3-bromo-4,5-dihydroisoxazole compds. were prepared and tested for their ability to irreversibly inhibit human transglutaminase 2 (TG2), an enzyme that plays an important role in the pathogenesis of diverse disorders including Celiac Sprue and certain types of cancers. Several compds. showed high specificity for human TG2 (kinh/KI > 2000 min-1M-1) but essentially no reactivity (k < 1 min-1M-1) toward physiol. thiols such as glutathione. The pharmacokinetic and pharmacodynamic properties of a prototype dihydroisoxazole inhibitor, 1b, were evaluated; in mice the compound showed good oral bioavailability, short serum half-life and efficient TG2 inhibition in small intestinal tissue, and low toxicity. It

also showed excellent synergism with N,N'-bis(2-chloroethyl)-N-nitrosourea (BCNU, carmustine) against refractory glioblastoma tumors in mice. A fluorescent dihydroisoxazole inhibitor 5 facilitated microscopic visualization of TG2 endocytosis from the extracellular surface of HCT-116 cells. Together, these findings demonstrate the promise of dihydroisoxazole compds. as probes for the biol. of TG2 and its role in human disease.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 15 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 15
ACCESSION NUMBER: 2005:101544 HCAPLUS
DOCUMENT NUMBER: 142:232941
TITLE: Prolyl endopeptidase-mediated destruction of T cell epitopes in whole gluten: Chemical and immunological characterization
AUTHOR(S): Marti, Thomas; Molberg, Oyvind; Li, Qing; Gray, Gary M.; **Khosla, Chaitan**; Sollid, Ludvig M.
CORPORATE SOURCE: Celiac Sprue Research Foundation, Palo Alto, CA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 312(1), 19-26
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Celiac Sprue** is a widely prevalent immune disease of the small intestine induced by dietary gluten intake in genetically susceptible individuals. It has been suggested that prolyl endopeptidases (PEPs) may be useful catalysts for gluten detoxification. We have investigated this hypothesis using food-grade gluten as the target antigen, and a combination of mass spectrometry and patient-derived T cells as quant. assay systems. Spectrometric characterization of physiol. proteolyzed gluten revealed a number of 10 to 50 residue peptides containing known T cell epitopes involved in **Celiac Sprue** pathogenesis. Several of these peptides were multivalent, suggesting they may be potent triggers of the inflammatory response to gluten in celiac patients. Treatment of proteolyzed gluten with recombinant bacterial PEP decreased the number of potentially immunostimulatory peptides. Substantially reduced immunogenicity was also quantified in 12 of 14 intestinal polyclonal T cell lines from celiac patients. Kinetic investigations using eight T cell clones showed rapid destruction of α-gliadin epitopes, but less complete processing of γ-gliadin epitopes. Given the difficulty associated with a strict lifelong gluten-exclusion diet, the ability of a single enzyme to greatly reduce the antigenic burden of grocery store gluten reinforces the case for developing oral peptidase therapy against **Celiac Sprue**

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 16 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 16
ACCESSION NUMBER: 2004:703116 HCAPLUS
DOCUMENT NUMBER: 141:218994
TITLE: Tissue transglutaminase (tTGase) inhibitor therapy for celiac sprue and dermatitis herpetiformis
INVENTOR(S): **Khosla, Chaitan; Choi, Kihang**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of Appl.

No. PCT/US03/15343.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004167069	A1	20040826	US 2003-716846	20031118
CA 2487247	AA	20031127	CA 2003-2487247	20030514
WO 2003096979	A2	20031127	WO 2003-US15343	20030514
WO 2003096979	A3	20040212		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003234597	A1	20031202	AU 2003-234597	20030514
EP 1507549	A2	20050223	EP 2003-728939	20030514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2005049064	A1	20050602	WO 2004-US37873	20041112
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2006035838	A1	20060216	US 2005-514177	20050628
US 2006052308	A1	20060309	US 2005-213173	20050826

PRIORITY APPLN. INFO.:

US 2002-380761P	P	20020514
US 2002-392782P	P	20020628
US 2002-422933P	P	20021031
US 2002-428033P	P	20021120
WO 2003-US15343	A2	20030514
US 2003-716846	A	20031118

OTHER SOURCE(S): MARPAT 141:218994

AB Administering an ED of a tTGase inhibitor to a celiac sprue or dermatitis herpetiformis patient reduces the toxic effects of toxic gluten oligopeptides, thereby attenuating or eliminating the damaging effects of gluten. Preparation and tissue transglutaminase-inhibiting activity of dihydroisoxazole moiety-containing compds. is included.

L42 ANSWER 17 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 17
ACCESSION NUMBER: 2004:292851 HCAPLUS
DOCUMENT NUMBER: 140:419555
TITLE: Structural basis for HLA-DQ2-mediated presentation of gluten epitopes in celiac disease

AUTHOR(S): Kim, Chu-Young; Quarsten, Hanne; Bergseng, Elin; **Khosla, Chaitan**; Sollid, Ludvig M.
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, CA, 94305, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2004), 101(12), 4175-4179
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Celiac disease, also known as **celiac sprue**, is a gluten-induced autoimmune-like disorder of the small intestine, which is strongly associated with HLA-DQ2. The structure of DQ2 complexed with an immunogenic epitope from gluten, QLQPFPQPELPY, has been determined to 2.2-Å resolution by x-ray crystallog. The glutamate at P6, which is formed by tissue transglutaminase-catalyzed deamidation, is an important anchor residue as it participates in an extensive hydrogen-bonding network involving Lys-β71 of DQ2. The gluten peptide-DQ2 complex retains critical hydrogen bonds between the MHC and the peptide backbone despite the presence of many proline residues in the peptide that are unable to participate in amide-mediated hydrogen bonds. Positioning of proline residues such that they do not interfere with backbone hydrogen bonding results in a reduction in the number of registers available for gluten peptides to bind to MHC class II mols. and presumably impairs the likelihood of establishing favorable side-chain interactions. The HLA association in celiac disease can be explained by a superior ability of DQ2 to bind the biased repertoire of proline-rich gluten peptides that have survived gastrointestinal digestion and that have been deamidated by tissue transglutaminase. Finally, surface-exposed proline residues in the proteolytically resistant ligand were replaced with functionalized analogs, thereby providing a starting point for the design of orally active agents for blocking gluten-induced toxicity.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 18 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 18
ACCESSION NUMBER: 2004:846854 HCAPLUS
DOCUMENT NUMBER: 141:325468
TITLE: Effect of prolyl endopeptidase on digestive-resistant gliadin peptides in vivo
AUTHOR(S): Piper, Justin L.; Gray, Gary M.; **Khosla, Chaitan**
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, CA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2004), 311(1), 213-219
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Many gluten peptides elicit proliferative responses from T cells from **Celiac Sprue** patients, influencing the pathogenesis of this small intestinal disorder. These peptides are Pro- and Gln-rich in character, suggesting that resistance to proteolysis promotes their toxicity. To test this hypothesis, we analyzed the digestive resistance of a panel of α- and γ-gliadin peptides believed to induce toxicity via diverse mechanisms. Most were highly resistant to gastric and pancreatic protease digestion, but they were digested by intestinal

brush-border peptidases. In some instances; there was accumulation of relatively long intermediates. Control peptides from gliadin and myoglobin revealed that digestive resistance depended on factors other than size. Prolyl endopeptidase (PEP) supplementation substantially reduced the concns. of these peptides. To estimate a pharmacol. useful PEP dose, recombinant PEP was coperfused into rat intestine with the highly digestive-resistant 33-mer peptide LQLQPF(PQPQLPY)3PQPQPF (PEP: peptide weight ratio 1:50 to 1:5). PEP dosing expts. indicate significant changes in the average residence time. The in vivo benefit of PEP was verified by coperfusion with a mixture of 33-mer and partially proteolyzed gliadin. These data verify and extend our earlier proposal that gliadin peptides, although resistant to proteolysis, can be processed efficiently by PEP supplementation. Indeed, PEP may be able to treat **Celiac Sprue** by reducing or eliminating such peptides from the intestine.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 19 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 19

ACCESSION NUMBER: 2003:249857 HCAPLUS
DOCUMENT NUMBER: 140:70705
TITLE: Design, Synthesis, and Evaluation of Gluten Peptide Analogs as Selective Inhibitors of Human Tissue Transglutaminase
AUTHOR(S): Hausch, Felix; Halttunen, Tuula; Maki, Markku; **Khosla, Chaitan**
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, CA, 94305, USA
SOURCE: Chemistry & Biology (2003), 10(3), 225-231
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent studies have implicated a crucial role for tissue transglutaminase (TG2) in the pathogenesis of Celiac Sprue, a disorder of the small intestine triggered in genetically susceptible individuals by dietary exposure to gluten. Proteolytically stable peptide inhibitors of human TG2 were designed containing acivicin or alternatively 6-diazo-5-oxo-norleucine (DON) as warheads. In biochem. and cell-based assays, the best of these inhibitors, Ac-PQP-(DON)-LPF-NH2, was considerably more potent and selective than other TG2 inhibitors reported to date. Selective pharmacol. inhibition of extracellular TG2 should be useful in exploring the mechanistic implications of TG2-catalyzed modification of dietary gluten, a phenomenon of considerable relevance in Celiac Sprue.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Some J Data pres. / not clear on Elected Comp. of Inv.

L42 ANSWER 20 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 20

ACCESSION NUMBER: 2002:879730 HCAPLUS
DOCUMENT NUMBER: 138:37933
TITLE: Circular dichroism and nuclear magnetic resonance spectroscopic analysis of immunogenic gluten peptides and their analogs
AUTHOR(S): Parrot, Isabelle; Huang, Philip C.; **Khosla, Chaitan**
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, CA, 94305-5025, USA
SOURCE: Journal of Biological Chemistry (2002), 277(47), 45572-45578
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Celiac Sprue**, or gluten-sensitive enteropathy, is an inheritable human disease of the small intestine that is triggered by the dietary intake of gluten. Recently, several Pro- and Gln-rich peptide sequences (most notably PQPQLPY and analogs) have been identified from gluten with potent immunogenic activity toward CD4+ T cells from small intestinal biopsies of **Celiac Sprue** patients. These peptides have 3 unusual properties. First, they are relatively stable toward further proteolysis by gastric, pancreatic, and intestinal enzymes. Second, they are recognized and deamidated by human tissue transglutaminase (**tTGase**) with high selectivity. Third, **tTGase**-catalyzed deamidation enhances their affinity for HLA-DQ2, the disease-specific class II major histocompatibility complex heterodimer. To seek a mechanistic explanation for these properties, the authors undertook secondary structural studies on PQPQLPY and its analogs. CD studies on a series of monomeric and dimeric analogs revealed a strong polyproline II helical propensity in a subset of them. Two-dimensional NMR spectroscopic anal. confirmed a polyproline II conformation of PQPQLPY, and was also used to elucidate the secondary structure of the most helical variant, (D-P)QPQLPY. Remarkably, a strong correlation was observed between polyproline II content of naturally occurring gluten peptides and the specificity of human **tTGase** toward these substrates. Analogs with up to two D-amino acid residues retained both polyproline II helical content and transglutaminase affinity. Since the Michaelis constant (Km) is the principal determinant of **tTGase** specificity for naturally occurring gluten peptides and their analogs, the authors' results suggest that the **tTGase** binding site may have a preference for polyproline II helical substrates. If so, these insights could be exploited for the design of selective small mol. inhibitors of this pharmacol. important enzyme.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 21 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 21
ACCESSION NUMBER: 2002:731653 HCAPLUS
DOCUMENT NUMBER: 138:3850
TITLE: Structural Basis for Gluten Intolerance in **Celiac Sprue**
AUTHOR(S): Shan, Lu; Molberg, Oyvind; Parrot, Isabelle; Hausch, Felix; Filiz, Ferda; Gray, Gary M.; Sollid, Ludvig M.; **Khosla, Chaitan**
CORPORATE SOURCE: Department of Chemical Engineering, Stanford Univ., Stanford, CA, 94305-5025, USA
SOURCE: Science (Washington, DC, United States) (2002), 297(5590), 2275-2279
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Celiac sprue**, a widely prevalent autoimmune disease of the small intestine, is induced in genetically susceptible individuals by exposure to dietary gluten. A 33-mer peptide was identified that has several characteristics suggesting it is the primary initiator of the inflammatory response to gluten in **celiac sprue** patients. In vitro and in vivo studies in rats and humans demonstrated that it is stable toward breakdown by all gastric, pancreatic, and

intestinal brush-border membrane proteases. The peptide reacted with tissue transglutaminase, the major autoantigen in **celiac sprue**, with substantially greater selectivity than known natural substrates of this extracellular enzyme. It was a potent inducer of gut-derived human T cell lines from 14 of 14 **celiac sprue** patients. Homologs of this peptide were found in all food grains that are toxic to **celiac sprue** patients but are absent from all nontoxic food grains. The peptide could be detoxified in in vitro and in vivo assays by exposure to a bacterial prolyl endopeptidase, suggesting a strategy for oral peptidase supplement therapy for **celiac sprue**.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 22 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 22
ACCESSION NUMBER: 2002:809931 HCAPLUS
DOCUMENT NUMBER: 138:220565
TITLE: Intestinal digestive resistance of immunodominant gliadin peptides
AUTHOR(S): Hausch, Felix; Shan, Lu; Santiago, Nilda A.; Gray, Gary M.; **Khosla, Chaitan**
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, CA, 94305-5025, USA
SOURCE: American Journal of Physiology (2002), 283(4, Pt. 1), G996-G1003
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two recently identified immunodominant epitopes from α-gliadin account for most of the stimulatory activity of dietary gluten on intestinal and peripheral T lymphocytes in patients with **celiac sprue**. The proteolytic kinetics of peptides containing these epitopes were analyzed in vitro using soluble proteases from bovine and porcine pancreas and brush-border membrane vesicles from adult rat intestine. The proline-glutamine-rich epitopes are exceptionally resistant to enzymic processing. Moreover, as estimated from the residual peptide structure and confirmed by exogenous peptidase supplementation, dipeptidyl peptidase IV and dipeptidyl carboxypeptidase I were identified as the rate-limiting enzymes in the digestive breakdown of these peptides. A similar conclusion also emerged from analogous studies with brush-border membrane from a human intestinal biopsy. Supplementation of rat brush-border membrane with trace quantities of a bacterial prolyl endopeptidase led to the rapid destruction of the immunodominant epitopes in these peptides. These results suggest a possible enzyme therapy strategy for **celiac sprue**, for which the only current therapeutic option is strict exclusion of gluten-containing food.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 23 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 23
ACCESSION NUMBER: 2001:889356 HCAPLUS
DOCUMENT NUMBER: 136:149679
TITLE: High Selectivity of Human Tissue Transglutaminase for Immunoactive Gliadin Peptides: Implications for **Celiac Sprue**
AUTHOR(S): Piper, Justin L.; Gray, Gary M.; **Khosla, Chaitan**
CORPORATE SOURCE: Departments of Chemical Engineering Medicine Chemistry

and Biochemistry, Stanford University, Stanford, CA, 94305-5025, USA
SOURCE: Biochemistry (2002), 41(1), 386-393
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Celiac Sprue** is an HLA-DQ2 (or -DQ8)-associated autoimmune disorder of the human small intestine that is induced by dietary exposure to wheat gliadin and related proteins from barley, rye, and possibly other food grains. Recently, tissue transglutaminase (**tTGase**)-catalyzed deamidation of gliadin peptides has been shown to increase their potency for activating patient-derived, gliadin-specific T cells, suggesting that **tTGase** plays a causative role in the onset of an inflammatory response to toxic food grains. To dissect the mol. recognition features of **tTGase** for gluten derived peptides, the regioselectivity and steady-state kinetics of **tTGase** -catalyzed deamidation of known immunogenic peptides were investigated. The specificity of recombinant human **tTGase** for all immunogenic peptides tested was comparable to and, in some cases, appreciably higher than the specificity for its natural substrate. Although each peptide was glutamine-rich, **tTGase** exhibited a high degree of regioselectivity for a particular glutamine residue in each peptide. This selectivity correlated well with Q → E substitutions that have earlier been shown to enhance the immunogenicity of the corresponding gliadin peptides. The specificity of **tTGase** toward homologues of PQPQLPY, a sequence motif found in immunodominant gliadin peptides, was analyzed in detail. Remarkably, the primary amino acid sequences of wheat-, rye-, and barley-derived proteins included many single-residue variants of this sequence that were high-affinity substrates of **tTGase**, whereas the closest homologues of this sequence found in rice, corn, or oat proteins were much poorer substrates of **tTGase** . (Rice, corn, and oats are nontoxic ingredients of the Celiac diet.). No consensus sequence for a high-affinity substrate of **tTGase** could be derived from our data, suggesting that the secondary structures of these food-grain peptides were important in their recognition by **tTGase**. Finally, under steady-state turnover conditions, a significant fraction of the **tTGase** active site was covalently bound to a representative high-affinity immunogenic gliadin peptide, suggesting a common mechanism by which cells responsible for immune surveillance of the intestinal tract recognize and generate an antibody response against both gliadin and **tTGase**. In addition to providing a quant. framework for understanding the role of **tTGase** in **Celiac Sprue**, our results lay the groundwork for the design of small mol. mimetics of gliadin peptides as selective inhibitors of **tTGase**.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 24 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:851500 HCAPLUS
TITLE: HLA-binding peptide inhibitors for diagnostic and therapeutic methods for **Celiac Sprue**
INVENTOR(S): **Khosla, Chaitan**; Xia, Jiang; Siegel, Matthew John
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior University, USA
SOURCE: U.S. Pat. Appl. Publ., 47pp., Cont.-in-part of U.S. Ser. No. 514,005.

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006189540	A1	20060824	US 2005-198068	20050804
WO 2003096984	A2	20031127	WO 2003-US15506	20030514
WO 2003096984	A3	20040701		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003234634	A1	20031202	AU 2003-234634	20030514
CA 2502700	AA	20040603	CA 2003-2502700	20031120
WO 2004045392	A2	20040603	WO 2003-US37434	20031120
WO 2004045392	A3	20040826		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003294473	A1	20040615	AU 2003-294473	20031120
EP 1563300	A2	20050817	EP 2003-789958	20031120
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005256054	A1	20051117	US 2005-514005	20050513

PRIORITY APPLN. INFO.:

US 2002-380761P	P	20020514
US 2002-392782P	P	20020628
US 2002-422933P	P	20021031
US 2002-428033P	P	20021120
WO 2003-US15506	W	20030514
WO 2003-US37434	W	20031120
US 2005-514005	A2	20050513
US 2005-531547	A2	20051116

AB The invention provides sequences of HLA-binding peptide inhibitors for diagnostic and therapeutic methods for **Celiac Sprue**. Detection of toxic gluten oligopeptides refractory to digestion and antibodies and T cells responsive thereto can be used to diagnose **Celiac Sprue**. Analogs of such oligopeptides are useful in the inhibition of immune responses.

L42 ANSWER 25 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:13178 HCAPLUS
DOCUMENT NUMBER: 144:81233
TITLE: Effect of prolyl endopeptidase on digestive-resistant

gliadin peptides in vivo and use for treating **Celiac Sprue** or **dermatitis herpetiformis** patient
INVENTOR(S): Piper, Justin L.; Gray, Gary M.; **Khosla, Chaitan A.**
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior University, USA
SOURCE: U.S. Pat. Appl. Publ., 28 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006002917	A1	20060105	US 2005-107539	20050415
PRIORITY APPLN. INFO.:			US 2004-565684P	P 20040426

AB Administering an ED of glutenase to a **Celiac Sprue** or **dermatitis herpetiformis** patient reduces levels of toxic gluten oligopeptides, thereby attenuating or eliminating the damaging effects of gluten.

L42 ANSWER 26 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1198684 HCAPLUS
DOCUMENT NUMBER: 143:452912
TITLE: Enzyme treatment of foodstuffs for **celiac sprue**
INVENTOR(S): Shan, Lu; Bethune, Michael; **Khosla, Chaitan**; Gass, Jonathan; Pyle, Gail G.; Gray, Gary M.; Isaacs, Indu; Strohmeier, Gregg
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior University, USA
SOURCE: U.S. Pat. Appl. Publ., 59 pp., Cont.-in-part of U.S. Ser. No.367,405.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005249719	A1	20051110	US 2004-969314	20041019
US 2003215438	A1	20031120	US 2003-367405	20030214
WO 2005107786	A1	20051117	WO 2005-US6129	20050223

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-357238P P 20020214
US 2002-380761P P 20020514

US 2002-392782P P 20020628
US 2002-422933P P 20021031
US 2002-428033P P 20021120
US 2002-435881P P 20021220
US 2003-367405 A2 20030214
US 2004-565668P P 20040426
US 2004-969314 A 20041019

AB The present invention relates to the discovery that certain gluten oligopeptides resistant to cleavage by gastric and pancreatic enzymes, that the presence of such peptides results in toxic effects, and that enzymic treatment can remove such peptides and their toxic effects. By digestion with glutenases, these toxic oligopeptides are cleaved into fragments, thereby preventing or relieving their toxic effects in **Celiac Sprue** or **dermatitis herpetiformis** patients. In some embodiments of the invention, the subject therapy comprises the steps of monitoring and/or diagnosis with assays for intestinal malabsorption and malfunction.

L42 ANSWER 27 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:834880 HCAPLUS
DOCUMENT NUMBER: 142:19039
TITLE: Comparative biochemical analysis of three bacterial prolyl endopeptidases: implications for coeliac sprue
AUTHOR(S): Shan, Lu; Marti, Thomas; Sollid, Ludvig M.; Gray, Gary M.; **Khosla, Chaitan**
CORPORATE SOURCE: Department of Chemical Engineering, Stanford University, Stanford, CA, 94305, USA
SOURCE: Biochemical Journal (2004), 383(2), 311-318
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prolyl endopeptidases have potential for treating **celiac sprue**, a disease of the intestine caused by proteolytically resistant peptides from proline-rich prolamins of wheat, barley and rye. We compared the properties of three similar bacterial prolyl endopeptidases, including the known enzymes from Flavobacterium meningosepticum (FM) and Sphingomonas capsulata (SC) and a novel enzyme from Myxococcus xanthus (MX). These enzymes were interrogated with reference chromogenic substrates, as well as two related gluten peptides (PQPQLPYPQPQLP and LQLQPFPQPQLPYPQPQLPYPQPQLPYPQPQPF), believed to play a key role in **celiac sprue** pathogenesis. In vitro and in vivo studies were conducted to evaluate the activity, specificity and acid/protease stability of the enzymes. All peptidases were relatively resistant to acid, pancreatic proteases and membrane peptidases of the small intestinal mucosa. Although their activities against reference substrates were similar, the enzymes exhibited substantial differences with respect to chain length and subsite specificity. SC hydrolyzed PQPQLPYPQPQLP well, but had negligible activity against LQLQPFPQPQLPYPQPQLPYPQPQLPYPQPQPF. In contrast, the FM and MX peptidases cleaved both substrates, although the FM enzyme acted more rapidly on LQLQPFPQPQLPYPQPQLPYPQPQLPYPQPQPF than MX. Whereas the FM enzyme showed a preference for Pro-Gln bonds, SC cleaved both Pro-Gln and Pro-Tyr bonds with comparable efficiency, and MX had a modest preference for Pro-(Tyr/Phe) sites over Pro-Gln sites. While a more comprehensive understanding of sequence and chain-length specificity may be needed to assess the relative utility of alternative prolyl endopeptidases for treating **celiac sprue**, our present work has illustrated the diverse nature of this class of enzymes from the

standpoint of proteolyzing complex substrates such as gluten.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 28 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:982884 HCAPLUS
TITLE: Chemistry Biology of **Celiac Sprue**
AUTHOR(S): **Khosla, Chaitan**
CORPORATE SOURCE: Departments of Chemistry, Chemical Engineering, and Biochemistry, Stanford University, Stanford, CA, 94305, USA
SOURCE: Abstracts, 56th Southeast Regional Meeting of the American Chemical Society, Research Triangle Park, NC, United States, November 10-13 (2004), GEN-243. American Chemical Society: Washington, D. C. CODEN: 69FWAQ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB **Celiac Sprue** is an autoimmune disorder that occurs as a result of dietary exposure to gluten, a complex mixture of nutritionally important proteins found in common foodgrains such as wheat, rye, and barley. Although the disease was considered uncommon until recently, several independent epidemiol. studies suggest that the prevalence of **Celiac Sprue** is 0.5-1% in North America and Europe. This is a life-long disease, and if untreated, patients have a substantially enhanced risk for the development of further complications such as infertility, osteoporosis and cancer. There is no therapeutic option available to **Celiac Sprue** patients, and the only treatment is a lifelong adherence to strict gluten exclusion. Since gluten is one of the most common ingredients in the human diet and is an unlabeled additive in many packaged foods, this is extremely difficult and often impractical. Using a combination of chemical and biol. approaches, we have analyzed the fundamental pathogenic mechanisms underlying this immune disorder, and are translating these insights into three different, and perhaps complementary, disease-specific therapeutic approaches. Recent progress in these fundamental and practical directions will be presented.

L42 ANSWER 29 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:656530 HCAPLUS
DOCUMENT NUMBER: 139:185696
TITLE: Enzyme treatment of foodstuffs for **celiac sprue**
INVENTOR(S): Hausch, Felix; Gray, Gary; Shan, Lu; **Khosla, Chaitan**
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior University, USA
SOURCE: PCT Int. Appl., 69 pp. CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068170	A2	20030821	WO 2003-US4743	20030214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2475972	AA 20030821	CA 2003-2475972	20030214
AU 2003215272	A1 20030904	AU 2003-215272	20030214
EP 1572127	A2 20050914	EP 2003-711089	20030214

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, FI, CY, TR, BG, CZ, EE, HU, SK

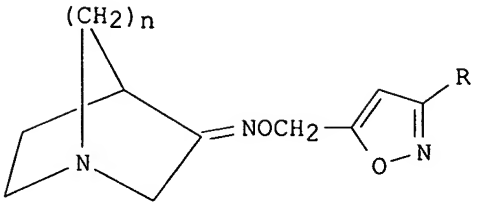
PRIORITY APPLN. INFO.:	US 2002-357238P	P 20020214
	US 2002-380761P	P 20020514
	US 2002-392782P	P 20020628
	US 2002-422933P	P 20021031
	US 2002-428033P	P 20021120
	US 2002-435881P	P 20021220
	WO 2003-US4743	W 20030214

AB Administering an ED of glutenase to a **celiac sprue** or **dermatitis herpetiformis** patient reduces levels of toxic gluten oligopeptides, thereby attenuating or eliminating the damaging effects of gluten.

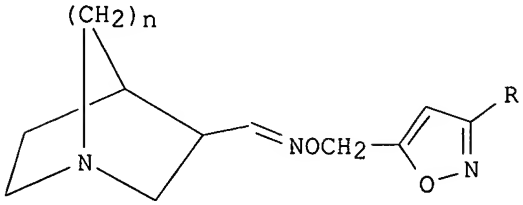
L42 ANSWER 30 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2001:746611 HCAPLUS
DOCUMENT NUMBER:	136:200126
TITLE:	Synthesis and in vitro binding affinities of 1-azabicyclic compounds as muscarinic ligands
AUTHOR(S):	Cha, J. H.; Cho, Y. S.; Pae, A. N.; Koh, H. Y.; Jeong, D.; Kong, J. Y.; Lee, E.; **Choi, K. I.**
CORPORATE SOURCE:	School of Chemistry and Molecular Engineering, Seoul National University, Seoul, 151-742, S. Korea
SOURCE:	Bioorganic & Medicinal Chemistry Letters (2001), 11(21), 2855-2857 CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER:	Elsevier Science Ltd.
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 136:200126

GI



HCl I



HCl II

AB Two series of compds., I and II [n = 1, 2, R = OMe, CN, Cl, Br], were synthesized and their binding affinities were evaluated for the human recombinant muscarinic M1 receptor subtype expressed in CHO cells. Comparing their binding affinities for the NMS binding sites and the Oxo-M binding sites, they were assumed as agonists. In particular, I [n = 1, R = Cl] was a good ligand for the agonist binding sites with an IC50 of 23 nM, which represents over 1585 times stronger binding than for the antagonist binding sites.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 31 OF 38 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:102255 HCAPLUS
DOCUMENT NUMBER: 134:326434
TITLE: Solution-phase combinatorial synthesis of isoxazolines and isoxazoles using [2+3] cycloaddition reaction of nitrile oxides
AUTHOR(S): Kang, K. H.; Pae, A. N.; **Choi, K. I.**; Cho, Y. S.; Chung, B. Y.; Lee, J. E.; Jung, S. H.; Koh, H. Y.; Lee, H.-Y.
CORPORATE SOURCE: Biochemical Research Center, KIST, Cheongyang, Seoul, S. Korea
SOURCE: Tetrahedron Letters (2001), 42(6), 1057-1060
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:326434

AB An efficient way to construct a library of isoxazoles and isoxazolines was developed by solution-phase 1,3-dipolar cycloaddn. reaction of nitrile oxides with olefins and alkynes followed by precipitation of the products as HCl salts.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 32 OF 38 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 87285695 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3613688

TITLE: Epidermal Langerhans cell density and contact sensitivity in young and aged BALB/c mice.
AUTHOR: **Choi K L**; Sauder D N
CONTRACT NUMBER: R01A604956
SOURCE: Mechanisms of ageing and development, (1987 Jun) Vol. 39, No. 1, pp. 69-79.
Journal code: 0347227. ISSN: 0047-6374.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198709
ENTRY DATE: Entered STN: 5 Mar 1990
Last Updated on STN: 5 Mar 1990
Entered Medline: 24 Sep 1987

AB The loss of tissue and organ function with age may depend on the inability of old cells to carry out specialized functions. Like other systems in the body, the immune system deteriorates with age. Over the past 10 years it has become clear that the skin can play an active role in immunological processes. In this report we evaluated changes in murine cutaneous immunity with age. Studies in humans had shown a decreased Langerhans cell density with age, but it is difficult to control for the effect of ultraviolet light in human studies. Since ultraviolet light has a significant effect on Langerhans cells, we chose to evaluate the effect of age on Langerhans cell density using inbred mice not exposed to ultraviolet light. Cutaneous immunity was examined phenotypically by studying Langerhans cell density and functionally by studying allergic contact sensitivity. Langerhans cell density was assessed in epidermal sheets prepared from ear skin of mice and examined by ATPase histochemistry and fluoresceinated anti-Ia staining. With both methods, aged (18 months old) mice had approximately two-thirds the number of Langerhans cells that young (10-12 weeks old) animals did. Allergic contact sensitivity response to trinitrochlorobenzene (TNCB) was compared between aged and young animals. Although the aged animals demonstrated increased variability in their responsiveness, there was no overall difference in this example of cutaneous immunoreactivity between the two age groups.

L42 ANSWER 33 OF 38 MEDLINE on STN
ACCESSION NUMBER: 86113800 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2418143
TITLE: The role of Langerhans cells and keratinocytes in epidermal immunity.
AUTHOR: **Choi K L**; Sauder D N
CONTRACT NUMBER: R01AGO4956 (NIA)
SOURCE: Journal of leukocyte biology, (1986 Mar) Vol. 39, No. 3, pp. 343-58. Ref: 122
Journal code: 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198603
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 26 Mar 1986

AB The immunology of the epidermis has received considerable study over recent years. After the antigen-presenting capacity of epidermal

Langerhans cells was confirmed, subsequent studies suggested that keratinocytes could modulate certain immunologic events through production of a cytokine, epidermal cell-derived thymocyte-activating factor (ETAF). Most recently, a murine epidermal cell population, the dendritic Thy-1-positive cell, has been shown to possess natural killer-cell-like activity. In this review, the biology of these cell types are discussed. A discussion of allergic contact hypersensitivity and its alteration by ultraviolet light is used to illustrate some of the complex control mechanisms that continue to be the subject of ongoing study.

L42 ANSWER 34 OF 38 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002332427 EMBASE
TITLE: Intestinal digestive resistance of immunodominant gliadin peptides.
AUTHOR: Hausch F.; Shan L.; Santiago N.A.; Gray G.M.; **Khosla C.**
CORPORATE SOURCE: C. Khosla, Stanford University, Dept. of Chemical Engineering, Keck Science Bldg., 380 Roth Way, Stanford, CA 94305-5025, United States. ck@chemeng.stanford.edu
SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology, (2002) Vol. 283, No. 4 46-4, pp. G996-G1003. .
Refs: 28
ISSN: 0193-1857 CODEN: APGPDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Oct 2002
Last Updated on STN: 3 Oct 2002

AB Two recently identified immunodominant epitopes from α-gliadin account for most of the stimulatory activity of dietary gluten on intestinal and peripheral T lymphocytes in patients with **celiac sprue**. The proteolytic kinetics of peptides containing these epitopes were analyzed in vitro using soluble proteases from bovine and porcine pancreas and brush-border membrane vesicles from adult rat intestine. We showed that these proline-glutamine-rich epitopes are exceptionally resistant to enzymatic processing. Moreover, as estimated from the residual peptide structure and confirmed by exogeneous peptidase supplementation, dipeptidy peptidase IV and dipeptidyl carboxypeptidase I were identified as the rate-limiting enzymes in the digestive breakdown of these peptides. A similar conclusion also emerged from analogous studies with brush-border membrane from a human intestinal biopsy. Supplementation of rat brush-border membrane with trace quantities of a bacterial prolyl endopeptidase led to the rapid destruction of the immunodominant epitopes in these peptides. These results suggest a possible enzyme therapy strategy for **celiac sprue**, for which the only current therapeutic option is strict exclusion of gluten-containing food.

L42 ANSWER 35 OF 38 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2006:246994 BIOSIS
DOCUMENT NUMBER: PREV200600247981
TITLE: Chemistry and biology of human transglutaminase 2: its role in **celiac sprue** and other diseases.
AUTHOR(S): **Khosla, C.** [Reprint Author]

CORPORATE SOURCE: Stanford Univ, Dept Chem, Stanford, CA 94305 USA
khosla@stanford.edu
SOURCE: FEBS Journal, (JUL 2005) Vol. 272, No. Suppl. 1, pp. 408-409.
Meeting Info.: 30th Congress of the Federation-of-European-Biochemical-Societies (FEBS)/9th IUBMB Conference. Budapest, HUNGARY. July 02 -07, 2005. Federat European Biochem Soc; Int Union Biochem Mol Biol.
ISSN: 1742-464X. E-ISSN: 1742-4658.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Apr 2006
Last Updated on STN: 26 Apr 2006

L42 ANSWER 36 OF 38 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:208563 BIOSIS
DOCUMENT NUMBER: PREV200600210292
TITLE: Capacity of Prolyl Endopeptidases (peps) to cleave a panel of gluten peptides toxic to the **Celiac Sprue** small intestine.
AUTHOR(S): Ehren, Jennifer; Gray, Gary; **Khosla, Chaitan**
SOURCE: Gastroenterology, (APR 2005) Vol. 128, No. 4, Suppl. 2, pp. A254.
Meeting Info.: Annual Meeting of the American-Gastroenterological-Association/Digestive-Disease-Week. Chicago, IL, USA. May 14 -19, 2005. Amer Gastroenterol Assoc.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Mar 2006
Last Updated on STN: 29 Mar 2006

AB Oral Prolyl Endopeptidase (PEP) is a promising therapeutic approach in aiding digestion of gluten in **Celiac Sprue** patients. An inflammatory and possibly autoimmune response develops in a **Celiac Sprue** patient's small intestine in response to consumption of wheat (gluten), barley, and rye proteins. Recent studies demonstrate the ability of PEP to break down the non-digestible gliadin peptides from whole gluten into nontoxic peptide fragments. Current research goals encompass detailed evaluation of cleavage of a panel of previously determined toxic gluten peptide T cell epitopes by two PEP enzymes. The epitope bearing peptides PQPQLPYPQPQLP, PFPQPQLPYPQ, SQPQQQFPQPQQPQ PQQSFPQQQ, IQPQQPAQL, QQPQQPYPQ, LQPQQPFPQQPQ PFPQPQQQF, PFSQQQQPV, and two longer, physiologically relevant peptides PFPQPQLPYPQPQLPYPQPQLPYPQPQP and FLQPQQPFPQQPQQPYPQQPQQPFPQ were synthesized and evaluated. The capacities of two PEP enzymes from Flavobacterium meningosepticum and Myxococcus xanthus were determined. Preliminary data indicates that both PEP enzymes have greater specificity for alpha-gliadin epitopes than gamma-gliadin epitopes. Cleavage sites and specificity for individual peptide epitopes differ between the two enzymes. Comparison of the two enzymes will lead to the choice of a superior oral therapeutic treatment option and subsequent engineering of that enzyme.

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ACCESSION NUMBER: 2002:508163 BIOSIS
DOCUMENT NUMBER: PREV200200508163
TITLE: Structural and mechanistic studies on the interactions between human tissue transglutaminase and immunodominant peptides: Implications for **celiac sprue**
.
AUTHOR(S): Piper, Justin L. [Reprint author]; Parrot, Isabelle [Reprint author]; Kim, Chu-Young [Reprint author]; Huang, Philip C. [Reprint author]; Hausch, Felix [Reprint author]; **Khosla, Chaitan** [Reprint author]; Gray, Gary M. [Reprint author]
CORPORATE SOURCE: Stanford, CA, USA
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A.15. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 2002
Last Updated on STN: 2 Oct 2002

L42 ANSWER 38 OF 38 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:518865 BIOSIS
DOCUMENT NUMBER: PREV200200518865
TITLE: Digestive resistance of immunodominant gliadin peptides: Implications for enzyme therapy in **Celiac Sprue**.
AUTHOR(S): Hausch, Felix [Reprint author]; Santiago, Nilda A. [Reprint author]; **Khosla, Chaitan** [Reprint author]; Gray, Gary M. [Reprint author]
CORPORATE SOURCE: Stanford, CA, USA
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A-180. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Oct 2002
Last Updated on STN: 9 Oct 2002